

REMARKS

Claims 36-37 and 41-45 stand rejected under 35 U.S.C. §103(a) over Dorigatti et al. (Dorigatti).

Reconsideration is requested in view of these4 Remarks and the attached Declaration of Giovanni Abatangelo. The Dorigatti patent is concerned with hyaluronic acid (HA) total or partial esters. The particular esters are described as having different degrees of esterification and are taught as being useful for processing into non-woven fabrics. These non-woven fabrics are for use as skin coverings or as buffer media in surgery of nose and inner ear.

Dorigatti reports 26 Examples that are concerned both with the preparation of HA total esters and of HA partial esters. Examples 12 and 14 disclose the preparation of the HA total benzyl ester.

Examples 27-31 of Dorigatti describe non-woven fabrics made of partial or total esters. Examples 27 and 31 disclose non-woven fabrics made of HA total benzyl ester and Example 29 refers to a non-woven fabric made of HA total benzyl ester mixed with HA total ethyl ester, and Example 30 refers to a non woven fabric made of HA total benzyl ester mixed with HA partial benzyl ester with esterification degree of 75% in a proportion of 1:1, so that the degree of esterification of the resulting product is 87.5%.

The present invention, as pointed out by the amended claims, is concerned with the use of a HA partial benzyl ester having an esterification degree of 65%. this amendment is supported by the original disclosure, particularly at page 9, line 4.

The Examples of Dorigatti do not disclose the partial benzyl ester of HA defined in the claims of the present application. In addition, there is no teaching in Dorigatti that a 65% benzyl ester of HA has special advantages as compared to other partial benzyl esters of HA. The 65% benzyl ester of HA is novel as it is not disclosed nor suggested by

Dorigatti wherein the total benzyl ester of HA was prepared in Examples 12 and 14, and a non-woven fabric made of HA total benzyl ester or of HA partial benzyl ester with an esterification degree of 87.5% was disclosed in Examples 27 and 29-31.

Claim 1 only relates to biomaterials free from cellular components made from hyaluronic acid benzyl ester having an esterification degree of 65% and processed in the form of non-woven tissue or biomaterials made of hyaluronic acid esters and processed in the form of three-dimensional structures enclosing hollow spaces formed by communicating pores.

when the presently claimed biomaterials are in the form of non-woven tissue, they are made of benzyl esters of hyaluronic acid, whereas when they are in the form of three-dimensional structures enclosing hollow spaces formed by communicating pores, they are made of esters of hyaluronic acid wherein part or all of the carboxy functions are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series.

Dorigatti only relates to biomaterials in the form of non-woven tissues, the other form claimed in the present application being neither taught nor suggested by Dorigatti.

As concerns to the present biomaterials in the form of non-woven tissues, claim 1 only refers to those non-woven tissues made of hyaluronic acid benzyl esters having an esterification degree of 65%.

As correctly noted by the Examiner, Dorigatti disclose also the preparation of hyaluronic acid esters having an esterification degree lower than 65% (see Examples 1, 2 and 8). Besides the observations already submitted that they are different from benzyl esters and they are salified in the non

esterified groups and are not in the form of non-woven tissues.

In particular, the Examiner is requested to consider that Examples 27 and 31 relate to non woven fabrics made of HA total benzyl ester, Example 29 refers to a non woven fabric made of HA total benzyl ester mixed with HA total ethyl ester, and Example 30 refers to a non woven fabric made of HA total benzyl ester mixed with HA partial benzyl ester with a degree of esterification of 75% in a proportion of 1:1, so that the degree of esterification of the resulting product is 87.5%.

For these reasons, it is evident that Dorigatti teaches the preparation of esters of hyaluronic acid having various degrees of esterification and the preparation of non woven tissues made of benzyl esters of hyaluronic acid having a degree of esterification from 75% to 100%. Moreover, even if Dorigatti mention the possible use of HA esters as buffer media in surgery to the nose and inner ear or as skin coverings, this cannot be considered as a motivation for the skilled person to make the present benzyl ester having a specific esterification degree of 65% in order to get an improved material for regeneration of mammal tissue.

In fact, nothing in the broad teachings of Dorigatti directs the skilled artisan to select and use an HA with 65% esterification from the possible HA esters described by Dorigatti. Actually, even though Dorigatti teaches the use of fully esterified HA benzyl esters or highly esterified HA the Applicant surprisingly found that an esterification of 65% of the carboxy groups of HA gives unexpected results in regenerating tissues.

In the attached Declaration of Giovanni Abatangelo, three Experiments were reported which were carried out to compare HA woven fabrics with HA having 65% esterification, 80% esterification and 100% esterification.

Experiment 1 in the attached Abatangelo declaration substantially corresponds to the experiment described in Example 1 of the present specification and Graph 1 in the Declaration corresponds to Graph 1 of the present specification. The results of this experiment show that the biomaterial made of benzyl ester of hyaluronic acid having an esterification degree of 65% and processed in the form of non-woven tissue, is superior to the other biomaterials made of totally esterified hyaluronic acid or made of esters having esterification degree higher than 65%, such as those disclosed in Dorigatti, when used for bone regeneration in a rat model. In particular, from Graph 1 it is evident that the percentage of newly formed bone is substantially higher when the present benzyl ester HYAFF 11p65 having a degree of esterification of 65% is used than in the case where the biomaterial is made of the corresponding total ester HYAFF 11 prepared according to Examples 12, 14, 27, 29 and 31 of Dorigatti.

Experiment 2 in the Abatangelo Declaration substantially corresponds to the experiment described in Example 2 of the present specification and Graph 2 in the Abatangelo Declaration corresponds to Graph 2 of the present specification. The results of this experiment show that the claimed biomaterial made of benzyl ester of hyaluronic acid having an esterification degree of 65% and processed in the form of non-woven tissue, is superior to the other biomaterials made of totally esterified hyaluronic acid, such as those disclosed in Dorigatti, when used for re-epithelialization in a pig model. In Graph 2, the percentage of re-epithelialization is illustrated for the presently claimed non-woven tissue made of HYAFF 11p65 in comparison with the corresponding HA derivative totally esterified HYAFF 11 of Dorigatti, and the superiority of the expewriment according to the claimed invention is readily apparent.

Experiment 3 refers to the claimed biomaterials made of hyaluronic acid esters processed in the form of three-dimensional structures enclosing hollow spaces formed by communicating pores. The results of this experiment show the efficacy of these biomaterials when used as implants for the treatment of osteochondral defects in rabbit.

The data reported in the Abatangelo Declaration is persuasive of the unexpected results that are obtained by using the 65% esterified HA. The reported results could not have been predicted and rebut any inference of obviousness based on the Dorigatti patent. For these reasons, it is requested that this ground of rejection be withdrawn.

The Examiner rejected claims 36, 37 and 41-45 as being unpatentable for obviousness double patenting over claims 14, 15 and 1 of U.S. Patent No. 6,509,322 (the '322 patent) in view of Dorigatti.

Reconsideration is requested.

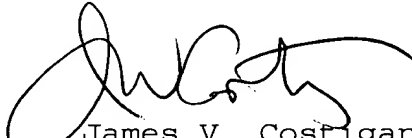
The claims of the '322 patent teach a method of accelerating tissue repair in an open wound comprising treating a tissue of said open wound with an effective amount of hyaluronic acid that has been esterified or partially esterified with an alcohol in a gaseous vehicle, a pharmaceutically acceptable carrier wherein the composition is in the form of a dry spray or foam.

The composition disclosed by the claims of the '322 patent is completely different from a three dimensional structure enclosing hollow spaces formed by communicating pores or from a non-woven tissue useful for regenerating tissues, for example for repairing bone defects. As it is clearly stated in the '322 claims, the composition of the invention always contains a gaseous vehicle.

Moreover, a skilled person would not have any incentive to combine the teachings of the claims of the '322 patent with Dorigatti, because while both patents teach the use the respective product for treating damaged tissues, the products disclosed in the two patents are completely different between each other to the extent that the composition disclosed by the '322 patent could never be used for the use mentioned by Dorigatti (as buffer media in surgery to the nose and inner ear or as skin coverings) and the non-woven esters of Dorigatti cannot be used for the applications taught by the claims of the '322 patent which are limited to applications involving a dry spray or a foam. For these reason, the rejection for double patenting in error and should be withdrawn.

An early and favorable action is earnestly solicited.

Respectfully submitted


James V. Costigan
Registration No.: 25,669

MAILING ADDRESS
HEDMAN & COSTIGAN, P.C.
1185 Avenue of the Americas
New York, N.Y. 10036
(212) 302-8989

I hereby certify that this
correspondence is being
deposited with the United States Postal Service as
first class mail in an envelope addressed to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
7/1/04
